REMARKS/ARGUMENTS

Applicants respectfully request that the Examiner reconsider the subject application in view of the amendments and the following remarks.

In the Office Action dated April 6, 2004, the Examiner requests that Applicants cancel claims 28-29. In response to this suggestion, claims 28-29 has been canceled. In addition, the Examiner alleges that claims 28-34 have been misnumbered, and should renumber as claims 30-36. However, since the original claims 28-29 have been cancelled, there is no need to move the originally added claims 30-34 to claims 32-36. Therefore, Applicants decide to leave the previously added claims 30-34 with the same numbers. The Examiner is welcome to discuss the renumbering matter with Applicants' counsel any time should he believe that the numbering should be done in other way.

In addition to the cancellation of claims 28-29, Applicants have converted claim 6 into an independent claim, which particularly claim the excipient as chitosan. Applicants further amended claims 13 to incorporate the limitations of claim 15 into the claim. As a result, claims 14-15 are cancelled. Furthermore, claims 16 and 17 are amended to incorporate the limitations of the original claim 13 into the claims. As a result, two additional claims, *i.e.*, claims 35 and 36, are added, which are essentially the same as the combined claims 19-20, due to the amendment of claim 13. No new matter has been introduced.

Claims 1-10, 12-20, and 26-27 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Gala et al. U.S. 5,478,571 (Gala) in combination with Bai U.S. 5,840,329 (Bai). Claims 30-36 (which in view of this response, stays as claims 28-34) are rejected under

under 35 U.S.C. § 103(a) as being unpatentable over Gala in combination with Bai, and further in view of Bahia et al. U.S. 6,075,177 (Bahia).

Applicants respectfully traverse these rejections for the reasons set forth in the following sections.

Claims 35-36 (which in this case stay as claims 33-34) are further rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because the term "water absorbing property" is not defined. In response to these rejections, Applicants have amended claim 33 (which is claim 35 based on the Examiner's assertion) to incorporate the definition from claim 1, which recites that water absorbing property is "characterized by the presence of a methoxy alkylcarboxyl ($-CH_2-O-RCOO^-A^+$) group in said excipient; wherein R is a lower alkyl group having 1-4 carbon atoms; wherein A^+ is Na^+ or K^+," into claim 33. Applicants respectfully submit that the amendment of claim 33 has obviated the 112 rejection.

Rejections – 35 U.S.C. § 103(a)

Claims 1-10, 12-20, and 26-27 are rejected under 35 U.S.C. . § 103(a) as being unpatentable over Gala et al. U.S. 5,478,571 (Gala) in combination with Bai U.S. 5,840,329 (Bai).

Specifically, the Examiner alleges that "Gala teaches methods to remove residual solvent alcohols without adverse affects **to the drug** by adding a small amount of water (col. 2, lines 24-30) ..... Gala teaches that the excipient blend of **conventional** carrier materials can be lactose, microcrystalline cellulose and cornstach (col. 3, lines 28-33)." (emphasis added); (See Final Office Action at page 3-4,¶ 8). In addition, the Examiner alleges that "Bai teaches that

carboxymethylcellulose and sodium starch glycolate, polysaccharide with water-absorbing properties (*i.e.*, containing $-CH_2$-O-R-COO^-A^+ moieties), are known as inert pharmaceutical excipients." Thus, the Examiner concludes that "[i]t would have been obvious to one of ordinary skill in the art to use the method of Gala to reduce the residual solvent content of **any known drug/excipient system**. Therefore, a skilled artisan would have been motivated .... to use any known **conventional excipient** .... in the method provided by Gala to obtain the low-residual-solvent excipient claimed in the present invention. Further, **the choice of solvent and reaction conditions**, i.e., temperature and agitation methods, are seen to be a choice of experimental design, are well known to one of ordinary skill and are well within the purview of the prior art." (emphasis added); (See Final Office Action at pages 5-6. ¶ 8).

Applicants incorporate by reference their earlier responses to the arguments.

Additionally, Applicants respectfully traverse the Examiner's arguments for the following reasons:

First, the Examiner has completely missed the true meaning of the claimed invention. With regard to Gala, it is clear that Gala does not teach a low-residual-solvent excipient, rather, it discloses a drug composition or a formulation containing a water-insoluble drug (See col. 2, lines 22-24 and lines 35-41) and an excipient blend of **conventional pharmaceutical carrier materials** consisting of lactose (65-70% w/w), microcrystalline cellulose (15-25% w/w) and corn starch (8-12% w/w). (See col. 3, lines 29-34). The water-insoluble drug is required to be first dissolved in an organic solvent so as to facilitate the uniform dispersion of the drug among the excipients. As described by Gala, "[t]here exist many water-insoluble drugs which must be dissolved in organic solvents in order to uniformly disperse them throughout an inert carrier

material. Obviously however, once the dispersion has been carried out, the organic solvent must be removed whereby the dissolved drug becomes solidified as particulate matter within the matrix system." (See col. 2, lines 35-41). Thus, it is clear that the goal of Gala is to remove the excess solvent from the drug, NOT from the excipients, which is contrary to Applicants' invention, where the focus is on the removal of the residual solvent that is left within the excipient. An excipient is defined as "any more or less inert substance added to a prescription in order to confer a suitable consistency or form to the drug; a vehicle." (See Dorland's Illustrated "Medical Dictionary", 26th Edition, B.W. Saunders Company). Thus, clearly it is not a drug and shall not be generalized as a drug composition or drug/excipient system, as characterized by the Examiner in his argument regarding Gala. In fact, there is no limitation that Applicants' excipient must be used with either water-soluble or water-insoluble drug. Thus, in the case a water-soluble drug is involved, Gala's invention is not even applicable. Therefore, Gala is not an analogous art to Applicants' claimed invention and should not be considered to be prior art for the purpose of establishing obviousness.

Secondly, Applicants' excipient is NOT a conventional excipient, while Gala clearly teaches the use of conventional excipients, which effectively has "taught away" from Applicants' claimed invention. Applicants claim a low-residual-solvent excipient, which is characterized by its containing of less than 3000 ppm of solvent and possession of water absorbing property.

The Examiner's citations of col. 2, lines 24-30, col. 3, lines 45-57, and col. 3, lines 28-33, of Gala to support his contention that Gala teaches an excipient containing less than 3000 ppm of solvent is misplaced. As acknowledged by the Examiner, Gala teaches a drug carrier blend (*i.e.*, drug/excipient system), NOT an excipient alone. Even if a drug carrier blend contains less than

3000 ppm of solvent, it does not mean that each of the excipients in the drug carrier blend contains less than 3000 ppm of solvent. For example, if in a drug/excipient blend system where the drug takes up 70% by weight of the composition, and three excipients, each containing 10% by weight of the composition, a 1000 ppm of solvent in the composition could mean that no solvent is remained in the drug, but a possible 10,000 ppm of solvent is remained in one particular excipient if all solvent shifts to this excipient, or 3,333 ppm of each excipient, if the residual solvent distributes equally among the three excipients.

Furthermore, a conventional excipient, by definition, is an excipient that can be readily bought in the market. At the present time, no conventional excipients except the ones manufactured by Applicants, as indicated in Table 3 of the application, contain less than 3000 ppm of solvent. For example, the conventional market products for sodium starch glycolate, as illustrated in Table 3 of the present application on page 12, include EXPLOTAB® (which contains 41712/498 ppm of residual ethanol/ethyl acetate); PRIMOJEL® (which contains 20299 ppm of residual ethanol); TABLO® (which contains 4575 ppm of residual ethanol); VIVASTAR® P 5000 (which contains 346/10175 ppm of ethanol/methanol); VIVASTAR® (which contains 5666 ppm of methanol), all contain residual solvent more than 3000 ppm. And the reason why these excipients contain high-residual-solvent, even though the solvent is hazardous to human health, is simply because the solvent embedded in the sodium starch glycolate is difficult to be removed. Thus, the Examiner has not fulfilled his burden of proving a *prima facie* case that a "conventional" excipient used in Gala contains, as alleged by the Examiner, less than 3000 ppm of solvent.

The method cited by the Examiner to support his assertion that Gala teaches methods to remove residual solvent alcohols is also misplaced. (See col. 2, lines 24-30). These methods are designed to remove solvent altogether from a drug/excipient system, NOT from the excipient per se. The Examiner has not fulfilled his duty of proving that the same methods used by Gala to remove the solvent from the drug/excipient system can be used to remove solvent from the particular excipient alone. In fact, judging from the fundamental structural and physical differences between the drug used in Gala, which is water-insoluble, and the excipient claimed by Applicants, which possesses water absorbing property, it does not appear that the solvent removal principle used in Gala can be applied to the excipient claimed by Applicants.

Additionally, the Examiner's arguments that "the choice of solvent and reaction conditions [in Applicants' claimed invention], *i.e.*, temperature and agitation methods, are seen to be a choice of experimental design, are well known to one of ordinary skill and are well within the purview of the prior art," is without merits. To establish a *prima facie* case of obviousness under 35 U.S.C. § 103(a), the prior art reference must teach or suggest all the claim limitations. *See* M.P.E.P. § 706.02(j), citing In re Vaeck, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). Thus, it does not matter whether an ordinary skill in the art's choice of experimental design is, if the element(s) taught in the claim is completely missing in the prior art, the Examiner has not fulfilled his burden of establishing the *prima facie* case.

Finally, as acknowledged by the Examiner, Gala does not disclose each of the particular polysaccharide claimed or excipients with water-absorbing properties (See Final Office Action at page 4). Without knowing the water-absorbing properties of the excipient, the Examiner is now asking an ordinary skill in the art to guess or conduct undue experimentation to determine the

solvent ratios and/or reaction conditions, which is definitely not a reason in determining obviousness.

The Examiner's citation (col. 8, lines 12-39) of Bai in support of his notion that polysaccharides with water-absorbing properties (i.e., containing CH_2-O-R-COO^-A^+ moieties), are known as inert pharmaceutical excipients is also misplaced. The two paragraphs of Bai cited by the Examiner teach nothing but conventional binders. Nothing about excipient with less than 3000 ppm of solvent, or water-absorbing property, is mentioned in these two paragraphs. Applicants invite the Examiner to particularly point out where his notion of polysaccharides with water-absorbing properties can be found in the excerpts.

Because (1) as for the independent claims 1 and 6, none of Gala and Bai teaches a low-residual-solvent excipient (particularly containing less than 3000 ppm of solvent and possessing water-absorbing properties), and (2) as for the amended claims 13, 16, and 17, the combined teaching of Gala and Bai failed to disclose a unique combination of solvent and water to be used in removing the residual solvent from the excipient, Applicants' claimed invention is not obvious over Gala in combination with Bai. Applicants respectfully request that the rejections be withdrawn.

Rejections – 35 U.S.C. § 103(a)

Claims 30-36 (*i.e.*, present claims 30-34 due to cancellation of the previous claims 28-29) are rejected under 35 U.S.C. § 103(a) as being unpatentable over Gala in combination with Bai and further in view of Bahia. Specifically, the Examiner alleges that "[n]either Gala nor Bai explicitly teach the synthesis of low-residual-solvent excipient (*i.e.*, synthesis of

carboxymethylcellulose). However, their synthesis is well-known in the art as shown by Bahia." (See Final Office Action at page 8). Additionally, the Examiner asserts that "Bahia teaches that carboxymethylcellulose is prepared by reacting cellulose with a strong alkali and with monochloroacetic acid or a salt thereof (col. 3, lines 11-13; col. 4, lines 5-16)." (See Final Office Action at page 9).

As shown in the previous section, *supra*, the combined teachings of Gala and Gai do not teach a low-residual-solvent excipient containing less than 3000 ppm of solvent and possessing water-absorbing properties, and also do not teach a process of making the low-residual-solvent excipient containing the use of a unique combination of solvent and water solution. The addition of Bahia does not bridge the gap by providing the missing elements of Applicants' claimed invention. Especially, Bahia is an unanalogous art. It teaches carboxymethlcellulose filaments as tow or strand of textile filaments at least 15 mm long or a fabric of textile filaments at least 3 mm long. (See Abstract of Bahia). It does not teach carboxymethylcellulose to be used as an excipient, and certainly it does not concern about the reduction of the residual solvent in the excipient. In fact, as shown in col. 3, lines 23-25, the preferred solvents for producing the cellulose filaments are tertiary amine N-oxides, which is not used in Applicants' claimed invention (*i.e.*, claims 13, 16 and 17). Because the combination of Gala, Bai, and Bahia do not teach all of the claimed elements, Applicants' claimed invention is not obvious over Gala, Bai, and Bahia. Applicants respectfully request that the Examiner withdraw the rejections.

In view of the foregoing, the rejections have been overcome and the claims are in condition for allowance, early notice of which is requested. Should the application not be passed for issuance, the examiner is requested to contact the applicant's attorney to resolve the problem.

Respectfully submitted,

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